

Express Mail Label No. EV710806095US **10/552571**

JC05 Rec'd PCT/PTO 11 OCT 2005

Attorney Docket No. PB60213

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP04/04001	13 April 2004	15 April 2003

TITLE OF INVENTION

**NEW PROCESS FOR IMPROVING THE MANUFACTURE OF CLAVAMS, E.G.
CLAVULANIC ACID**

APPLICANT(S) FOR DO/US

Barry BARTON, Susan JENSEN, Alison Michelle GRIFFIN and Annie WONG

FILING OF AN INFORMATION DISCLOSURE STATEMENT

Applicants request that the references identified on Form PTO-1449 appended hereto be considered by the Examiner and officially made of record in accordance with the provisions of 37 CFR 1.97

A copy of the International Search Report, which issued on International Application No. PCT/EP04/04001 is submitted herewith. All of the publications cited in the International Search Report are listed on the attached form PTO-1449 and Applicants understand that copies have been supplied to the U.S. Patent Office by the International Bureau.

Copies of references not listed on the International Search Report are enclosed.

The attached list of citations on PTO Form 1449 is being submitted under the provisions of 37 CFR §1.56 and §1.97 in order to comply with the duty of disclosure. Their inclusion herein should not, however, be construed as an admission that any particular cited reference is effective prior art or that it discloses or renders obvious any aspect of the claimed invention. Applicants respectfully requests the Examiner initial the enclosed PTO Form 1449 indicating that the references have been considered and return said form to the undersigned attorney. This statement is being filed within the time period specified in 37 CFR §1.97(b). No fee is required.


Respectfully submitted,
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Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. PB60213	INTERNATIONAL APPLICATION NO. PCT/EP04/04001 10/552571
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use several sheets if necessary)</i>		APPLICANT Barry BARTON, Susan JENSEN, Alison Michelle GRIFFIN and Annie WONG	
		FILING DATE Herewith	GROUP

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
AA	4,202,819	5/13/80	Kellett <i>et al.</i>	260	245.3	

FOREIGN PATENT DOCUMENTS

	Document Number	Date	Country	Class	Subclass	Translation Yes No
BA	WO98/33896	06 Aug 1998	PCT			
BB	WO01/30977	03 May 2001	PCT			
BC	WO03/040372	15 May 2003	PCT			
BD	WO00/03581	27 Jan. 2000	PCT			
BE	JP 53-104796	12 Sept 1978	Japan			
BF	ES 550549	1987	Spain			
BG	EP 0 550549	20 Sept 1990	EP			
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CA	Liras P., et al., "Clavulanic acid, a β -lactamase inhibitor: biosynthesis and molecular genetics," <i>Applied Microbiology and Biotechnology</i> , Springer Verlag Berlin, Germany (2000) 54(4):467-475.
CB	Mosher R., et al., "Genes Specific for the Biosynthesis of Clavam Metabolites Antipodal to Clavulanic Acid are Clustered with the Gene for Clavaminic Synthase 1 in Streptomyces Clavuligerus," <i>Antimicrobial Agents and Chemotherapy</i> , American Society for Microbiology, Washington, DC (May 1999) 43(5):1215-1224.
CC	A.L. Demain, "Biosynthesis and Regulation of Beta-Lactam Antibiotics", <i>50 Years of Penicillin Applications, History & Trends</i> (1990).
CD	Townsend, et al., "Biosynthesis of clavulanic Acid: Origin of the C ₃ Unit," <i>J. Am. Chem. Soc.</i> , 107(4):1066-1068 (1985).
CE	Valentine, et al., "Evidence that Arginine is a Later Metabolic Intermediate than Ornithine in the Biosynthesis of Clavulanic Acid by Streptomyces Clavuligerus," <i>J. Chem. Soc. Chem. Comm.</i> , 15:1210-1211 (1993).

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Form PTO-1449	U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. PB60213	INTERNATIONAL APPLICATION NO. PCT/EP02/04001 107552571
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)		APPLICANT Barry BARTON, Susan JENSEN, Alison Michelle GRIFFIN and Annie WONG	FILING DATE Herewith
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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

CF	Janc, et al., "Emerging Evidence for a Shared Biosynthetic Pathway Among Clavulanic Acid and the Structurally Diverse Clavam Metabolites," <i>Bioorg. Med. Chem. Lett.</i> , 3:2313-2316 (1993).
CG	Rohl, et al., "Biological properties and mode of action of clavams," <i>Arch. Microbiol.</i> , 147:315-320 (1987).
CH	Aidoo, et al., "Cloning, sequencing and disruption of a gene from <i>Streptomyces clavuligerus</i> involved in clavulanic acid biosynthesis," <i>Gene</i> , 147:41-46 (1994).
CI	Sambrook, et al., <i>Molecular Cloning: A Laboratory Manual, 2nd Edition</i> . Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989).
CJ	"Postassium Clavulanate," <i>British Pharmacopoeia</i> (1993); Addendum (1994) pp. 1362-1363.
CK	"Clavulanate Potassium," <i>British Pharmacopoeia Official Monographs, USP 23 NF18</i> pp: 384-385 (1985).
CL	Hopwood, et al., <i>Genetic Manipulation of Streptomyces. A Cloning Manual</i> (1985).
CM	Stahl, et al., "Development and Application of Nucleic Acid Probes," <i>Nucleic Acid Techniques in Bacterial Systematics</i> . Ed. E. Stackebrandt & M. Goodfellow. Toronto: John Wiley & Sons, pp. 204-248 (1991).
CN	Doran, et al., "Isolation and Characterization of a β -Lactamase-Inhibitory Protein from <i>Streptomyces Clavuligerus</i> and Cloning and Analysis of the Corresponding Gene," <i>J. Bacteriol.</i> 172(9):4909-4918 (1990).
CO	Vieira, et al., "Production of Single-Stranded Plasmid DNA," <i>Methods Enzymol.</i> , 153: 3-11 (1987).
CP	Sanger, et al., "DNA Sequencing with Chain-terminating Inhibitors," <i>Proc. Natl. Acad. Sci. USA</i> , 74: 5463-5467 (1977).
CQ	Ward, et al., "Construction and Characterisation of a Series of Multi-Copy Promoter-Probe Plasmid Vectors for <i>Streptomyces</i> Using the Aminoglycoside Phosphotransferase Gene from Tn5 as Indicator," <i>Mol. Gen. Genet.</i> 203: 468-478 (1986).
CR	Pruess, et al., "A New Clavam Antibiotic from <i>Streptomyces Clavuligerus</i> ," <i>Journal of Antibiotics</i> , XXXVI(3): 208-212 (Mar. 1983).
CS	Paradkar, et al., "Functional analysis of the Gene Encoding the Clavaminate Synthase 2 Isoenzyme Involved in Clavulanic Acid Biosynthesis in <i>Streptomyces Clavuligerus</i> ," <i>Journal of Bacteriology</i> , 177: 1307-1314 (1995).
CT	Hodgson, J.E. et al., "Clavulanic Acid Biosynthesis in <i>Streptomyces Clavuligerus</i> : Gene Cloning and Characterization," <i>Gene</i> , (1995) Vol. 166, pp. 49-55

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(Use several sheets if necessary)		FILING DATE Herewith	GROUP

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

CU	Busby, R.W., "Expression and Purification of Two Isozymes of Clavaminate Synthase and Initial Characterization of the Iron Binding Site," <i>J. Biological Chem.</i> , (1995), Vol. 270(9), pp. 4262-69
CV	Brown, D. et al., "Structures of Three Novel β -lactams Isolated from Streptomyces Clavuligerus," <i>J.C.S. Chem. Comm.</i> , (1979), pp. 282-3
CW	Marsh, E.N. et al., "Two Isozymes of Clavaminate Synthase Central to Clavulanic Acid Formation: Cloning and Sequencing of Both Genes from Streptomyces Clavuligerus," <i>Biochemistry</i> , (1992), Vol. 31, pp. 12648-57
CX	Elson, et al., "Studies on the Biosynthesis of Clavulanic Acid." <i>J. Antibiotics</i> , XXXI(6): 568 (1978)
CY	Evans, R. H. et al., "Ro 22-5417, A New Clavam Antibiotic from Streptomyces Clavuligerus II. Fermentation, Isolation and Structure" <i>J. Antibiotics</i> , (1983), Vol. 36(3), pp. 213-216
CZ	Muller, J-C. et al., "Ro 22-5417, A New Clavam Antibiotic from Streptomyces Clavuligerus III Absolute Stereochemistry," <i>J. Antibiotics</i> , (1983), Vol. 36(3), pp. 216-224
CAA	King, H.D. et al., "Clavamycins, New Clavam Antibiotics from Two Variants of Streptomyces Hygroscopicus I. Taxonomy of the Producing Organisms, Germination, and Biological Activities," <i>J. Antibiotics</i> , (1986), Vol. 39(4), pp. 510-15
CBB	Janc, J.W. et al., "Purification and Characterization of Clavaminate Synthase from Streptomyces Antibioticus," <i>J. Biological Chem.</i> , (1995), Vol. 270(10), pp. 5399-5404
CCC	Iwata-Reuly, D. and C. A. Townsend, "Common Origin of Clavulanic Acid and Other Clavam Metabolites in Streptomyces," <i>J. Am. Chem. Soc.</i> , (1992), Vol. 114, pp. 2762-3
CDD	Paradkar, A. S. and S. E. Jensen, "Functional Analysis of the Gene Encoding the Clavaminate Synthase 2 Isoenzyme Involved in Clavulanic Acid Biosynthesis in Streptomyces Clavuligerus," <i>J. Bacteriology</i> , (1995), Vol 177(5), pp. 1307-14
CEE	Baldwin, J. E. et al., "Enzymes of Valcalavam Biosynthesis," <i>Tetrahedron Letters</i> , (1994), Vol. 35(17), pp. 2783-6
CFF	Egan, L.A. et al., "Probable Role of Clavaminic Acid as the Terminal Intermediate in the Common Pathway to Clavulanic Acid and the Antipodal Clavam Metabolites," <i>J. Am. Chem. Soc.</i> , (1997), Vol. 119, pp. 2348-55

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